

What is claimed is:

1. A method of stimulating stem cell recruitment, proliferation, or differentiation to stimulate myelopoiesis comprising,
5 identifying a mammalian subject in need of stem cell recruitment, proliferation, or differentiation to treat, prevent, or reduce myelosuppression, and administering to the mammalian subject a composition comprising a vascular endothelial growth factor B (VEGF-B) product, in an amount effective to stimulate myelopoiesis in the subject.
- 10 2. The method of claim 1, wherein the mammalian subject is human.
3. The method of claim 1 or 2, wherein the identifying comprises selecting a subject undergoing antineoplastic chemotherapy.
- 15 4. The method of claim 3, wherein the administering comprises administering the composition contemporaneously with, or after, administering the antineoplastic chemotherapy.
5. The method of claim 1 or 2, wherein the identifying comprises selecting a bone marrow transplant subject.
- 20 6. The method of claim 5, wherein the administering comprises administering the composition contemporaneously with, or after, the bone marrow transplant.
7. The method of claim 1 or 2, wherein the identifying comprises selecting a subject undergoing antineoplastic radiation therapy.
- 25 8. The method of claim 7, wherein the administering comprises administering the composition contemporaneously with, or after, administering the radiation therapy.
9. The method of claim 1 or 2, wherein the identifying comprises:
measuring circulating white blood cells or bone-marrow derived stem cells in the subject to screen for myelosuppression.
- 30 10. The method of claim 9, wherein the measuring comprises measuring CD34+ stem cells.

11. The method of claim 9, wherein the measuring comprises measuring hematopoietic stem cells.

12. The method of any one of claims 1-11, wherein the method further comprises monitoring the number of circulating white blood cells or bone-marrow derived stem cells after administration of the composition.

13. The method of claim 12, wherein the monitoring comprises detection of at least one cell surface marker selected from the group consisting of VEGFR-1, VEGFR-2, and CD34.

14. The method of any one of claims 1-13, further comprising administering to said subject an agent selected from the group consisting of:

(a) granulocyte colony stimulating factor (G-CSF), macrophage-CSF (M-CSF), granulocyte-macrophage-CSF (GM-CSF), interleukin-3 (IL-3), stem cell factor (SCF), vascular endothelial growth factor (VEGF), vascular endothelial growth factor C (VEGF-C), vascular endothelial growth factor D (VEGF-D), platelet derived growth factor A (PDGF-A), platelet derived growth factor B (PDGF-B), platelet derived growth factor C (PDGF-C), platelet derived growth factor D (PDGF-D), and placental growth factor (PIGF);

(b) a polynucleotide comprising a nucleotide sequence encoding any member of (a), and

(c) combinations thereof.

15. A method of stimulating stem cell proliferation or differentiation, comprising,

obtaining a biological sample from a mammalian subject, wherein said sample comprises stem cells, and

contacting the stem cells with a composition comprising a vascular endothelial growth factor B (VEGF-B) product.

16. The method according to claim 15, further comprising a step of purifying and isolating the stem cells after obtaining the sample and before the contacting step.

17. The method according to claim 15 or 16, further comprising a step of purifying and isolating the stem cells after the contacting step.

18. The method according to claim 17, wherein the purified stem cells comprise VEGFR-1+ stem cells.

5 19. The method according to claim 17 or 18, wherein the purified stem cells comprise CD34+ stem cells.

20. The method according to any one of claims 17-19, wherein the purified stem cells comprise CD133+ stem cells.

10 21. The method according to any one of claims 15-20, wherein the contacting comprises culturing the stem cells in a culture containing the VEGF-B product.

22. The method according to any one of claims 15-21, further comprising a step of returning the stem cells to the mammalian subject.

15 23. The method according to any one of claims 15-22, further comprising a step of transplanting the cells into a different mammalian subject.

24. The method of claim 22 or 23, wherein the cells are seeded into a tissue, organ, or artificial matrices ex vivo, and said tissue, organ, or artificial matrix is attached, implanted, or transplanted into the mammalian subject.

20 25. The method according to any one of claims 15-24, wherein the mammalian subject is human.

26. The method according to any one of claims 15-25, wherein the human subject needs antineoplastic chemotherapy.

25 27. The method of claim 26, wherein the biological sample is obtained prior to administering a dose of chemotherapy, and wherein the stem cells are returned to the human subject after the contacting and after the dose of chemotherapy.

28. The method according to any one of claims 1-14 and 15-27, wherein the VEGF-B product comprises a VEGF-B polypeptide.

29. The method of claim 28, wherein the VEGF-B is glycosylated.

30. The method of any one of claims 1-14 and 15-27, wherein the VEGF-B product comprises a polynucleotide that encodes a VEGF-B polypeptide.

31. The method of claim 30, wherein the VEGF-B product comprises a viral vector containing the polynucleotide.

5 32. The method of claim 31, wherein the vector comprises a replication-deficient adenoviral or adeno-associated viral vector.

33. The method of any one of claims 28-32, wherein the VEGF-B polypeptide comprises the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, or a fragment thereof that binds VEGFR-1.

10 34. The method of claim 28 or 29, wherein the VEGF-B polypeptide is associated as a heterodimer with a VEGF polypeptide.

35. The method of claims 1-34, wherein the VEGF-B polypeptide binds VEGFR-1 and is encoded by a polynucleotide that hybridizes under stringent conditions with the complement of the polynucleotide in SEQ ID NO: 1 or 3.

15 36. The method of any one of claims 1-35, wherein the VEGF-B product further comprises a pharmaceutically acceptable carrier.

37. A method of stimulating stem cell recruitment, proliferation, or differentiation comprising,

20 identifying a mammalian subject in need of stem cell recruitment, proliferation, or differentiation to treat or prevent ischemia, and

administering to the subject a composition comprising a platelet derived growth factor (PDGF) product.

38. The method of claim 37, wherein the subject is human.

25 39. The method of claim 37 or 38, wherein the PDGF product comprises at least one member selected from the group consisting of PDGF-A, PDGF-B, PDGF-C, and PDGF-D products.

40. The method of claim 37 or 38, wherein the PDGF product binds PDGFR- α .

30 41. The method of claim 37 or 38, wherein the PDGF product comprises at least a PDGF-C product.

42. The method of claim 37 or 38, wherein the PDGF product comprises a PDGF polypeptide.

43. The method of claim 37 or 38, wherein the PDGF product comprises a polynucleotide that encodes a PDGF polypeptide.

5 44. The method of claim 43, wherein the PDGF product comprises a viral vector containing the polynucleotide.

45. The method of claim 44, wherein the vector comprises a replication-deficient adenoviral or adeno-associated viral vector.

46. The method of any one of claims 42-45, wherein the PDGF
10 polypeptide comprises a portion of the amino acid sequence set forth in SEQ ID NO: 7 or 9 that is effective to bind PDGFR-alpha or PDGFR-beta.

47. The method of any one of claims 42-45, wherein the PDGF polypeptide binds PDGFR-alpha or PDGFR-beta and is encoded by a polynucleotide that hybridizes under stringent conditions with the complement of the polynucleotide
15 in SEQ ID NO: 6 or 8.

48. The method of any one of claims 37 or 38, wherein the PDGF polypeptide comprises a member selected from the group consisting of a PDGF-A polypeptide, a PDGF-B polypeptide, a PDGF-C polypeptide, a PDGF-D polypeptide, combinations thereof, or fragments thereof that bind to at least one of PDGF receptors
20 alpha and beta (PDGFR-alpha, PDGFR-beta).

49. The method of any one of claims 37 or 38, wherein the PDGF polypeptide comprises a PDGF-C or PDGF-D polypeptide or a fragment thereof that binds to at least one of PDGF receptors alpha and beta (PDGFR-alpha, PDGFR-beta).

50. The method of any one of claims 37-49, wherein the
25 composition further comprises a pharmaceutically acceptable carrier.

51. The method of any one of claims 37-50, further comprising administering to said subject an agent selected from the group consisting of:

(a) granulocyte colony stimulating factor (G-CSF), macrophage-CSF (M-CSF), granulocyte-macrophage-CSF (GM-CSF), interleukin-3 (IL-3), stem
30 cell factor (SCF), vascular endothelial growth factor (VEGF), vascular endothelial growth factor B (VEGF-B) vascular endothelial growth factor C (VEGF-C), vascular

endothelial growth factor D (VEGF-D), platelet derived growth factor A (PDGF-A), platelet derived growth factor B (PDGF-B), platelet derived growth factor C (PDGF-C), platelet derived growth factor D (PDGF-D), and placental growth factor (PIGF);

(b) a polynucleotide comprising a nucleotide sequence encoding
5 any member of (a), and

(c) (c) combinations thereof.

52. A method of stimulating stem cell proliferation or differentiation, comprising,

obtaining a biological sample from a mammalian
10 subject, wherein said sample comprises stem cells, and

contacting the stem cells with a composition comprising a platelet derived growth factor C (PDGF-C) product or platelet derived growth factor D (PDGF-D) product.

53. The method according to claim 52, further comprising
15 contacting the cells with at least one additional PDGF product selected from the group consisting of a PDGF-A product, a PDGF-B product, a PDGF-C product and a PDGF-D product.

54. The method according to claim 52, further comprising a step of isolating the stem cells after obtaining the sample and before the contacting step.

20 55. The method according to claim 52, further comprising a step of purifying and isolating the stem cells after the contacting step.

56. The method according to claim 55, wherein the purified stem cells comprise cells that express PDGFR-alpha.

25 57. The method according to claim 55 or 56, wherein the purified stem cells comprise CD34+ stem cells.

58. The method according to any one of claims 52 and 53-57, wherein the contacting comprises culturing the stem cells in a culture containing the PDGF-C product or PDGF-D product.

59. The method according to any one of claims 52 and 53-58, further comprising a step of returning the stem cells to the mammalian subject after the contacting step.

60. The method according to any one of claims 52 and 53-58,
5 further comprising a step of transplanting the cells into a different mammalian subject after the contacting step.

61. The method of claim 59 or 60, wherein the cells are seeded into a tissue, organ, or artificial matrix ex vivo, and said tissue, organ, or artificial matrix is attached, implanted, or transplanted into the mammalian subject.

10 62. The method according to any one of claims 52 and 53-61, wherein the mammalian subject is human.

63. The method according to any one of claims 52 and 53-62, wherein the human subject needs antineoplastic chemotherapy.

64. The method of claim 62, wherein the biological sample is
15 obtained prior to administering a dose of chemotherapy, and wherein the stem cells are returned to the human subject after the contacting and after the dose of chemotherapy.

65. The method of any one of claims claim 52-62, wherein the PDGF-C product or PDGF-D product comprises a PDGF-C polypeptide or PDGF-D
20 polypeptide.

66. The method of any one of claims 52-62, wherein the product comprises a polynucleotide that encodes a PDGF-C polypeptide or a PDGF-D polypeptide.

67. The method of claim 66, wherein the product comprises a viral
25 vector containing the polynucleotide.

68. The method of claim 67, wherein the vector comprises a replication-deficient adenoviral or adeno-associated viral vector.

69. The method of any one of claims 65-68, wherein the polypeptide comprises a portion of the amino acid sequence set forth in SEQ ID NO:
30 7 or 9 that is effective to bind PDGFR-alpha or PDGFR-beta.

70. The method of any one of claims 65-68, wherein the PDGF polypeptide binds PDGFR-alpha or PDGFR-beta and is encoded by a polynucleotide that hybridizes under stringent conditions with the complement of the polynucleotide in SEQ ID NO: 6 or 8.

5 71. The method of any one of claim 52 and 53-70, wherein the composition further comprises a pharmaceutically acceptable carrier.

72. The method of any one of claims 52 and 53-71, further comprising administering to said subject an agent selected from the group consisting of:

10 (a) granulocyte colony stimulating factor (G-CSF), macrophage-CSF (M-CSF), granulocyte-macrophage-CSF (GM-CSF), interleukin-3 (IL-3), stem cell factor (SCF), vascular endothelial growth factor (VEGF), vascular endothelial growth factor B (VEGF-B), vascular endothelial growth factor C (VEGF-C), vascular endothelial growth factor D (VEGF-D), platelet derived growth factor A (PDGF-A),
15 platelet derived growth factor B (PDGF-B), platelet derived growth factor C (PDGF-C), platelet derived growth factor D (PDGF-D), and placental growth factor (PlGF);

(b) a polynucleotide comprising a nucleotide sequence encoding any member of (a), and

(c) combinations thereof.

20 73. The method of claim 54, wherein the isolating comprises isolating AC133+/CD34+ cells from the biological sample.

74. The method according to any one of claims 52 and 53-73, wherein the contacting comprises contacting the stem cells with the composition until stem cells differentiate into CD144+ cells.

25 75. The method according to any one of claims 52 and 53-73, wherein the contacting comprises contacting the stem cells with the composition until stem cells differentiate into SMA+/CD144-/CD31-/CD34- cells.

76. The method according to any one of claims 52 and 53-73, wherein the composition further comprises a VEGF-A product.

77. The method according to any one of claims 52 and 53-76, wherein the contacting comprises culturing the stem cells in a culture containing the PDGF-C product.

78. The method according to any one of claims 52 and 53-77,
5 further comprising a step of returning the stem cells to the mammalian subject after the contacting step.

79. The method of claim 78, wherein the cells are seeded into a tissue, organ, or artificial matrix ex vivo, and said tissue, organ, or artificial matrix is attached or implanted into the mammalian subject.

80. The method according to any one of claims 52 and 53-77,
10 further comprising a step of transplanting the cells into a different mammalian subject after the contacting step.

81. The method of claim 80, wherein the cells are seeded into a tissue, organ, or artificial matrix ex vivo, and said tissue, organ, or artificial matrix is
15 attached or transplanted into the different mammalian subject.

82. The method according to any one of claims 52 and 53-77, wherein the mammalian subject is human.

83. The method according to claim 82, wherein the human subject has an ischemic condition.

84. The method of claim 65, wherein the polypeptide comprises an amino acid sequence at least 95% identical to SEQ ID NO: 7 or 9 and binds to at least one receptor selected from PDGFR-alpha and PDGFR-beta.
20

85. The method of claim 65, wherein the polypeptide comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID
25 NO: 10 and binds to and/or activates at least one receptor selected from PDGFR- α/α and PDGFR- α/β .

86. The method of any one of claims 84 or 85, wherein the PDGF-C polypeptide binds PDGFR- α and is encoded by a polynucleotide that hybridizes under stringent conditions with the complement of the polynucleotide in SEQ ID NO:
30 6.

87. The method of claim 65, wherein the polypeptide binds PDGFR-alpha or PDGFR-beta and is encoded by a polynucleotide that hybridizes under stringent conditions with the complement of the polynucleotide of SEQ ID NO: 6 or 8.

5 88. A method of stimulating stem cell proliferation or differentiation, comprising,

obtaining a biological sample from a mammalian subject, wherein said sample comprises stem cells;

10 contacting a first aliquot of the stem cells with a first composition comprising a first growth factor product selected from a VEGF-B product and PDGF-C product; and

contacting a second aliquot of the stem cells with a second composition comprising a second growth factor product independently selected from the group consisting of VEGF-A, VEGF-B, VEGF-C, VEGF-D, PDGF-A, PDGF-B, PDGF-C, and PIGF products,

15 wherein the first and second growth factor products are not the same.

89. The method of claim 88, wherein the first growth factor product is a PDGF-C product and the second growth factor product is a VEGF-A product.

20 90. A method of promoting differentiation of stem cells into both endothelial and smooth muscle cells, comprising:

obtaining a biological sample from a mammalian subject, wherein said sample comprises stem cells; and

25 contacting the cells with a composition comprising a platelet-derived growth factor-C (PDGF-C) product, in an amount and for a time sufficient to cause the cells to differentiate into both endothelial and smooth muscle cells.

30 91. The method according to any of claims 88-90, further comprising returning the cells to the mammalian subject after the contacting.

92. The method of claim 91, wherein the mammalian subject has an ischemic condition.

93. A method of ameliorating an ischemic condition comprising:

(a) diagnosing a mammalian subject with an ischemic condition;

5 (b) isolating a biological sample from the mammalian subject, wherein the biological sample comprises stem cells;

(c) contacting the cells with a composition comprising a platelet-derived growth factor-C (PDGF-C) product, in an amount and for a time sufficient to cause the cells to differentiate into both endothelial and smooth muscle cells; and

10 (d) returning the cells to the mammalian subject.

94. The method according to claim 93, wherein the returning comprises implanting or injecting the cells into or adjacent to ischemic tissue of the mammalian subject.